Cardiac and Vascular Consequences of Pre-Hypertension in Youth

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Hypertension is associated with increased left ventricular mass (LVM) and carotid intima-media thickness (cIMT), which predict cardiovascular (CV) events in adults. Whether target organ damage is found in pre-hypertensive youth is not known. The authors measured body mass index, blood pressure, fasting glucose, insulin, lipids and C-reactive protein, LVM/height$^{2.7}$ (LVM index), diastolic function, cIMT, carotid stiffness, augmentation index, brachial artery distensibility, and pulse wave velocity (PWV) in 723 patients aged 10 to 23 years (29% with type 2 diabetes mellitus). Patients were stratified by blood pressure level (normotensive: 531, pre-hypertensive: 65, hypertensive: 127). Adiposity and CV risk factors worsened across blood pressure group. There was a graded increase in cIMT, arterial stiffness, and LVM index and decrease in diastolic function from normotension to pre-hypertension to hypertension. In multivariable models adjusted for CV risk factors, status as pre-hypertension or hypertension remained an independent determinant of target organ damage for LVM, diastolic function, internal cIMT, and carotid and arterial stiffness. Pre-hypertension is associated with cardiovascular target organ damage in adolescents and young adults. *J Clin Hypertens (Greenwich).* 2011;13: 332–342. ©2011 Wiley Periodicals, Inc.

Hypertension (HTN) is an established risk factor for target organ damage (TOD) in adults. High blood pressure (BP) is associated with increased left ventricular mass (LVM),[1] carotid intima-media thickness (cIMT),[2] and arterial stiffness.[3] Since TOD is known to predict hard cardiovascular (CV) events,[4–6] screening for TOD has become an established practice in preventive care for adults at risk for complications related to elevated BP.[7,8] Recent data suggest that no safe cutpoint for BP exists as pre-hypertension (pre-HTN) (between the 90th and 95th percentile for patients younger than 18 years or between 120/80 mm Hg and 140/90 mm Hg for adults) may progress to HTN[9] and TOD may begin at pre-hypertensive levels.[10] Studies in youth have documented TOD with sustained HTN,[11] but few data exist showing an increase in left ventricular hypertrophy in pre-HTN youth[12] and data on arterial abnormalities are lacking. Determining the prevalence of TOD in youth at borderline levels of BP is important since current pediatric guidelines[13] determine treatment levels based on arbitrary cutpoints without reference to hard CV events or intermediate noninvasive outcomes. Therefore, we performed noninvasive imaging in adolescents and young adults to determine whether TOD could be documented in pre-HTN patients before the onset of clinical HTN.

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METHODS

Study Population

These analyses were performed on data collected for a study that examined the effects of obesity and type 2 diabetes mellitus (T2DM) on CV structure and function. By design, one third of patients had T2DM (n=258), one third were obese ($\geq$95th percentile for body mass index [BMI]) but nondiabetic (n=234), and one third were lean (n=231 $<$85th percentile for BMI).[14] First, patients with T2DM (provider-diagnosed) were recruited from the Cincinnati Children's Hospital diabetes clinic (average duration of diabetes 3.6$\pm$2.6 years). Each diabetic patient was then matched by age, race, and sex to two controls (1 lean and 1 obese). All obese patients underwent a 2-hour oral glucose tolerance test to rule out subclinical T2DM according to American Diabetes Association guidelines.[15] Pregnant women were excluded from the study. The final study population consisted of 723 patients with a mean age of 18 years, 60% were non-Caucasian, 34% were men, and 29% had T2DM.

Prior to enrollment in the study, written informed consent was obtained from patients 18 years and older or the parent or guardian for patients younger than 18 years. Written assent was also obtained for patients younger than 18 years according to the guidelines established by the institutional review board at Cincinnati Children's Hospital.

Data Collection

After a minimum 10-hour overnight fast, participants had questionnaire, anthropometric, BP, laboratory, and arterial stiffness data collected. Trained personnel obtained two measures of height using a calibrated stadiometer (Veeder-Rood, Elizabethtown, NC). Each

patient's height was measured with the patient in the standing position wearing socks with heels together and toes apart at a 45° angle and the head in the Frankfort horizontal plane. Two height measurements were obtained with a third measurement taken if the first 2 were >0.5 cm apart. Weight was measured using a Health-o-meter electronic scale (Sunbeam Products, Inc, Boca Raton, FL). The scale was calibrated once per month and was used exclusively for this investigation. Two weight measurements were obtained. A third measurement was taken if the first two differed by >0.3 kg. BMI was calculated as kilograms per meters squared.

BPs were measured with mercury sphygmomanometery using a standardized protocol according to the standards of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[13] BP examiners were certified after receiving 16 hours of instruction and evaluation. Examiners were recertified annually. Participants were seated with feet resting flat on a surface and right arm resting at heart level. The appropriate cuff was selected based on arm circumference and placed around the upper arm. Using a standard mercury sphygmomanometer (Baum Desktop Model with V-Lok cuffs, New York, NY), 3 BPs were measured by rapidly inflating to the maximum inflation level and deflating at a rate of 2 mm Hg/s, with a 60-second rest between each determination. The first appearance of two consecutive beats determined the first Korotkoff phase (K1), the point at which a sound became muffled determined K4, and the point in which the sound disappeared determined K5. The pulse rate was measured for 30 to 60 seconds between BP determinations. Three BP measurements were obtained. The 3 BP determinations were averaged to calculate the mean systolic and diastolic BPs (K5). If any 2 of the 3 readings varied by >10 mm Hg, a fourth reading was performed and included in the average.

The mean of 3 resting measures was used. Patients were stratified as having normotension (NT=531), prehypertension (pre-HTN=65), or hypertension (HTN = 127) by BP level according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (based on sex, age, and height)[13] or the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) cutpoints[7] if they were 18 years or older.

Physical activity was assessed using an Actical accelerometer (Phillips Respironics, Andover, MA) worn on the waist during waking hours during a 7-day period. This device is an omnidirectional detector that provides counts of movement in all directions.[16] Counts of activity per minute worn were calculated and averaged during the 7 days.

Fasting plasma glucose was measured using a Hitachi model 704 glucose analyzer (Roche Hitachi, Indianapolis, IL) with intra-assay and interassay coefficients of variation of 1.2% and 1.6%, respectively.[17] Plasma insulin was measured by radioimmunoassay using an anti-insulin serum raised in guinea pigs, 125I labeled insulin (Linco Research, St Louis, MO), and a double antibody method to separate bound from free tracer. This assay has a sensitivity of 2 pmol and intra-assay and interassay coefficients of variation of 5% and 8%.[18] Assays of fasting plasma lipid profiles were carried out in a laboratory that was standardized by the National Heart, Lung, and Blood Institute and Centers for Disease Control and Prevention, with low-density lipoprotein (LDL) cholesterol concentration calculated using the Friedewald equation. High sensitivity C-reactive protein (CRP) was measured using a high-sensitivity enzyme-linked immunoabsorbent assay. Hemoglobin A_{1c} (HbA_{1c}) was measured in red blood cells using high-performance liquid chromatography methods.

Echocardiography Technique

Echocardiography was performed with a GE or Philips Sonos 5500 (Andover, MA) system with the patient in the left decubitus position. Parasternal long-axis, short-axis, and apical 4-chamber views were recorded, with 3 cardiac cycles averaged for each variable. Left ventricular end-diastolic dimension, end-systolic dimension, end-diastolic septal thickness, and end-diastolic and end-systolic posterior wall thicknesses were measured offline by either of two sonographers using a Cardiology Analysis System (Digisonics, Houston, TX). Left ventricular mass (LVM) was calculated with the formula of Devereaux and colleagues[19] and LVM index (LVMI=LVM/height$^{2.7}$) by De Simone's method.[20] Relative wall thickness (RWT) at end-diastole was also calculated. The cutpoints of 51 g/m$^{2.7}$ and a RWT of 0.41 were used to define geometry as described previously.[11]

For diastolic function, mitral inflow velocities were obtained with pulsed wave Doppler in the apical 4-chamber view. The Doppler cursor was placed parallel to mitral inflow, and maximal velocity was measured with the sample volume at the mitral valve leaflet tips. The mitral peak E (early filling) and A (inflow with atrial contraction) waves were measured offline and an E/A ratio was calculated. Myocardial flow velocities by tissue Doppler imaging were acquired in the apical 4-chamber view. The peak (Ea) and late velocities (Aa) of mitral annular flow were recorded at both the septal and lateral annulus and both lateral and septal Ea/Aa ratios and their average were calculated. Other diastolic variables that were calculated included E/Ea lateral and septal average and E over average of Ea/Aa ratio from the lateral and septal aspects of the valve.

Carotid Ultrasonography

Carotid ultrasonography studies were performed by a single registered vascular technologist with high-

resolution B-mode ultrasonography (GE Vivid7, Milwaukee, WI) with a high-resolution linear array vascular transducer (7.5 MHz). A 2-dimensional image of the carotid artery was obtained from the far wall for measurement of intima-medial thickness (IMT) in the common, bifurcation, and internal carotid segments. Then, images of the common carotid with both the near and far wall visualized were obtained for M-mode evaluation of peak and minimal diameters for calculation of arterial stiffness.[21] All digital images were read offline using the Camtronic Medical System software (Hartland, WI). Calculations included Peterson's elastic modulus (PEM)[22] and Young's elastic modulus (YEM).[23] Due to pulse wave amplification along the arterial tree resulting in overestimation of brachial systolic BP,[24] central BPs obtained with the SphygmoCor device (see arterial stiffness below) were used in the calculations of carotid stiffness. The central BPs were obtained, on average, no more than 30 minutes prior to the carotid ultrasound.

Arterial Stiffness Measurements

The average of 3 measurements of all vascular function measures were used in the analyses. Each measure was conducted after 5 minutes of rest in the supine position. A DynaPulse Pathway instrument (Pulse Metric, Inc, San Diego, CA) collected brachial artery distensibility (BrachD) as described previously.[25] This device derives brachial artery pressure curves from arterial pressure signals obtained from a standard cuff sphygmomanometer assuming a straight tube brachial artery and T-tube aortic system.[25] Repeat measures in our laboratory show excellent reproducibility with coefficients of variability $<9\%$.[26]

A SphygmoCor SCOR-PVx System (Atcor Medical, Sydney, Australia) was used for measurement of carotid-femoral pulse wave velocity (PWV) and augmentation index (AIx), an arterial stiffness measure incorporating features related to arterial stiffness and provides additional information concerning wave reflections.[27] This device employs a tonometer applied on the artery of interest to obtain electrocardiographic (ECG)-gated pressure data. PWV is calculated as the difference in the carotid-to-femoral path length (measured directly and entered into the device) divided by the difference in the R wave from the ECG to the foot of the pressure wave taken from the superimposed ECG and pressure tracings. For AIx, the pressure waves are calibrated using mean arterial pressure (MAP) and diastolic BP obtained in the same arm. A validated generalized transfer function is then applied for estimation of the central aortic pressure tracing and calculation of AIx.[28] Since AIx is affected by heart rate (HR), values are adjusted to a HR of 75 beats per minute. Repeat measures in our laboratory show excellent reproducibility with coefficients of variability $<7\%$ for PWV and intraclass correlation coefficients between 0.7 and 0.9 for AIx variables.[26]

Statistical Analysis

All analyses were performed with Statistical Analyses Software (SAS Institute Inc, version 9.2, Cary, NC).[29] Average values for demographic, anthropometric, and laboratory data were obtained by BP group. Analysis of variance was performed (or chi square analyses for categoric variables) to look for differences by BP group. Variance-stabilizing measures to transform non-normally distributed variables were performed as needed. Bivariate correlations were calculated between TOD measures and all covariates overall and by BP group. General linear models were constructed using important covariates from correlation analyses to determine whether BP group was an independent determinate of TOD even after inclusion of CV risk factors in the models.

The full model contained age, demographic (race, sex), anthropometric (waist/height ratio, BMI z score), hemodynamic (MAP to adjust for baseline distending pressure, HR except for the model for AIx, which is already adjusted for HR), laboratory (CRP and fasting LDL-C, HDL-C, triglycerides, glucose, insulin), T2DM, and physical activity (average activity counts per non-zero minute) measures. Total cholesterol was highly collinear with LDL cholesterol and HbA_{1c} with fasting glucose so these covariates were omitted to ensure stability of the models. Height was added to the model for AIx since height directly influences distance of wave reflection sites from the heart. Height is used in the calculations for BrachD and PWV so it was omitted from models for those outcomes. Significance of each covariate in the initial model was assessed and nonsignificant terms were removed by backward elimination until all remaining covariates or their interaction (effect modifier) terms were significant ($P<.05$).

The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the manuscript as written.

RESULTS

Patient characteristics are displayed in Table I. NT participants were slightly younger than pre-HTN and HTN patients. There were no differences in race but there were fewer men in the HTN group. The prevalence of T2DM and measures of adiposity and BP worsened from NT to pre-HTN to HTN. NT patients tended to have a better lipid profile, metabolic control, and level of inflammation than the other groups. HTN had the lowest activity levels (all $P\leq.05$ for comparisons listed above).

LVMI increased across the BP groups (Table II and Figure 1). HTN patients demonstrated a higher prevalence of abnormal geometry, 23.6% (for all abnormal patterns combined) compared with 7.7% for NT and pre-HTN ($P\leq.05$). There were no group differences in systolic function (shortening fraction, velocity of circumferential fiber shortening, or wall stress [data not shown]). NT patients had better diastolic function

TABLE I. Patient Characteristics by Blood Pressure Category

	NT (n=531)		Pre-HTN (n=65)		HTN (n=127)	
Variable	Mean	SD	Mean	SD	Mean	SD
Age, y[a]	17.4	3.1	19.3	3.5	20.0	3.1
Race, % non-Caucasian	58.0		58.5		70.9	
Sex, % male[b]	37.9		37.7		23.6	
Presence of T2DM, %[c]	21.9		40.0		55.9	
Height, cm[d]	166.8	10.6	166.3	9.1	167.1	10.6
Weight, kg[d]	82.6	28.2	94.9	28.8	108.7	31.2
Waist, cm[d]	96.1	22.3	108.0	23.3	118.6	23.0
Waist-height ratio[d]	0.58	0.13	0.65	0.14	0.71	0.13
BMI, kg/m^2[d]	29.4	9.3	34.1	9.3	38.7	9.8
SBP, mm Hg[d]	111.3	9.9	119.3	10.6	128.8	13.1
DBP, mm Hg[d]	61.5	11.7	67.9	11.1	72.9	14.6
MAP, mm Hg[d]	80.8	7.8	85.9	8.2	91.0	10.9
Heart rate, beats per min[a]	66.1	10.6	70.1	10.0	71.5	11.9
TC, mg/dL[a]	168.1	33.8	181.9	30.8	175.8	36.4
LDL-C, mg/dL[e]	98.4	28.8	109.2	28.4	103.6	29.7
HDL-C, mg/dL[f]	51.1	12.7	51.7	15.8	45.1	11.2
TG, mg/dL[a]	90.2	55.5	115.5	77.9	132.6	98.3
Glucose, mg/dL[g]	103.6	46.5	112.7	50.9	129.3	70.0
Insulin, μU/mL[h]	17.1	13.1	19.9	13.1	23.6	20.9
CRP, mg/L[a]	3.33	5.25	5.10	5.72	6.24	7.07
CPM, counts/non 0 min[f]	684	255	610	240	560	169

Abbreviations: BMI, body mass index; CPM, counts per minute; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; NT, normotension; SBP, systolic blood pressure; SD, standard deviation; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides. $P<.05$ for [a]NT<pre-HTN and HTN; [b]HTN<NT; [c]chi-square $P<.0001$ for difference in prevalence of type 2 diabetes mellitus by blood pressure group; [d]NT<pre-HTN<HTN; [e]NT<pre-HTN; [f]HTN<NT and pre-HTN; [g]NT and pre-HTN<HTN; [h]NT<HTN.

than HTN patients for all measures. Values for NT patients were also better than those for pre-HTN patients for mitral E/A ratio, TDI Ea/Aa septal ratio, average septal/lateral Ea/Aa ratios, and E/average Ea/Aa TDI lateral and septal ratios (all $P \leq .05$).

NT patients had significantly lower IMT than the other BP groups for the bulb and internal carotid artery segments and they had more flexible common carotid arteries as measured by PEM and YEM (Table III, Figure 2, and Figure 3, all $P \leq .05$). There was a graded increase in AIx and femoral PWV with a similar decrease in BrachD among the BP groups (Table III), indicating progressively stiffer vessels across the BP strata.

Multivariable models demonstrated that BP group remained a significant predictor of LVMI, E/Ea lateral ratio and average septal/lateral Ea/As, and E/average Ea/Aa TDI lateral and septal ratios (Table IV). BP group was also an independent predictor of (Table V) vascular damage for the internal cIMT, common carotid stiffness (PEM, YEM), AIx, BrachD, and PWV even after adjusting for CV risk factors and distending pressure (MAP). Plotting the age by BP group interaction for BrachD revealed a steeper decline in BrachD across BP groups for adolescents than young adults (data not shown).

DISCUSSION

Our data demonstrate that significant abnormalities in cardiac and vascular measures can be identified in youth with pre-HTN (increased LVM, carotid thickness, arterial stiffness, and decreased diastolic function). Although a deteriorating risk factor profile was seen across the BP distribution, the adverse cardiac and vascular changes are largely independent of other traditional CV risk factors. This is evident from the observation that classification as pre-HTN was an independent predictor of many measures of TOD (LVMI, E/Ea, average lateral-septal Ea/Aa, internal cIMT, PEM, YEM, AIx, BrachD, PWV) even after adjusting for CV risk factors including BMI and presence of T2DM. This suggests that even mild elevation in BP is an important etiology for TOD.

In hypertensive adults, elevated LVM is a well-described independent risk factor for adverse CV events[30] and is associated with development of depressed left ventricular (LV) systolic function, a precursor of heart failure.[31] Concentric hypertrophy, the geometric pattern most frequently seen in sustained HTN, is also associated with a poor prognosis.[32] However, cardiac abnormalities can be found in pre-hypertensive adults. Recent studies found depressed diastolic function in pre-hypertensives[33,34] and two large studies found higher LVM in these patients even after adjustment for other CV risk factors.[35,36] Pre-HTN may also lead to more age-related increases in LVM.[10] Furthermore, progression from pre-HTN to sustained HTN in the Strong Heart Study was predicted by both baseline systolic BP and also by baseline LVM,[37] with the probability of developing incident HTN increasing 36% for each standard deviation (SD) of LVMI.[38] The finding that development of mild LV thickening may accelerate progression to higher BP levels suggests that pre-HTN is not a benign condition.

LVH can also be identified in youth with HTN.[39,40] Using the adult cutpoint of 51 g/m$^{2.7}$, Daniels and colleagues found the prevalence for HTN-related LVH to be 8% in a clinic population,[11] while a multicenter study found the prevalence to be as high as 15.5%.[41] If the pediatric definition of ≥95th percentile of LVM is used, the prevalence may be as high as 30% to 40%.[41–43] Important epidemiologic studies of CV risk factors in youth also confirm a strong association between BP levels and LV thickness in non-hypertensive patients. The Muscatine Heart Study demonstrated that resting systolic BP exerted an independent

TABLE II. Cardiac Structure and Function by Blood Pressure Category

	Normal (n=531)		Pre-HTN (n=65)		HTN (n=127)	
Variable	Mean	SD	Mean	SD	Mean	SD
LVMI, g/m$^{2.7}$[a]	32.8	8.9	35.9	9.8	40.7	11.2
Relative wall thickness[b]	0.30	0.06	0.31	0.05	0.33	0.07
Geometry, No. (%)[c]						
Normal	490 (92.3)		60 (92.3)		97 (76.4)	
Concentric hypertrophy	19 (3.4)		2 (3.1)		6 (4.7)	
Eccentric hypertrophy	18 (3.4)		3 (4.6)		17 (13.4)	
Concentric remodeling	4 (0.8)		0 (0)		7 (5.5)	
Mitral Doppler E/A ratio[d]	2.02	0.55	1.86	0.51	1.82	0.46
Mitral Doppler E wave/TDI Ea lateral ratio[b]	5.71	1.44	6.01	1.65	6.70	1.51
Mitral Doppler E wave/TDI Ea septal ratio[e]	7.33	1.68	7.84	2.04	8.30	1.61
Mitral TDI lateral velocity Ea/Aa ratio[f]	2.74	0.87	2.56	0.77	2.36	0.69
Mitral TDI septal velocity Ea/Aa ratio[d]	2.07	0.62	1.82	0.49	1.68	0.52
Average Ea/Aa TDI lateral and septal ratios[g]	15.0	2.2	14.3	2.5	13.4	2.5
Mitral Doppler E wave/average Ea/lateral and Ea/septal tissue Doppler lateral and septal ratios[h]	6.36	1.37	6.74	1.64	7.33	1.36

Abbreviations: HTN, hypertension; LVMI, left ventricular mass index; NT, normotension; SD, standard deviation; TDI, tissue Doppler imaging. $P<.05$ for [a]NT<pre-HTN<HTN; [b]NT and pre-HTN<HTN; [c]chi-square $P\leq.0001$ for difference in geometry by blood pressure group; [d]NT<pre-HTN and HTN; [e]NT<HTN; [f]NT>HTN; [g]NT>pre-HTN>HTN; [h]NT>pre-HTN and HTN.

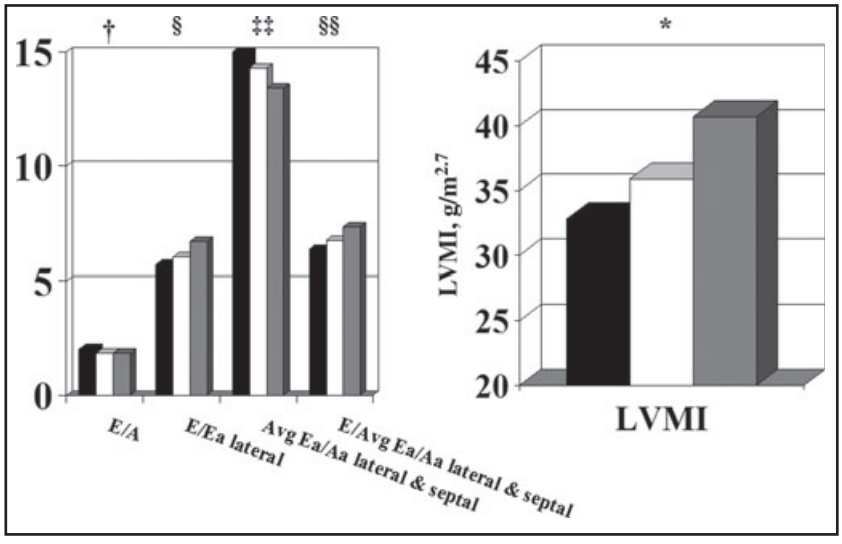

FIGURE 1. Cardiac structure and function by blood pressure group. LVMI indicates left ventricular mass index. $P<.05$ for *normotension (NT)<pre-hypertension (pre-HTN)<HTN; †NT<pre-HTN and HTN; §NT and pre-HTN<HTN; ‡‡NT>pre-HTN; §§NT>pre-HTN and HTN.

influence on LVM in children,[44] while the Bogalusa Heart Study found that the cumulative burden of systolic BP from childhood to adulthood was a significant predictor of LVMI in young adults.[45] Other cross-sectional studies of healthy children confirm the independent relationship between BP and LVM.[46,47] Therefore, it is not surprising that youth diagnosed with pre-HTN may also exhibit LVH,[12,48] with odds for having elevated LVMI increasing by 54% for each incremental increase in the SD score for 24-hour ambulatory systolic BP.[49] Higher ambulatory BP is also significantly associated with a higher prevalence of abnormal LV geometry in children and adolescents,[50] and BP also relates to left atrial diameter[51] and decreased diastolic function in youth.[52,53] Our data confirm the adverse effect of pre-hypertensive BP levels on LV structure and function in a larger cohort of adolescents and young adults.

As with LVM, carotid structure is also adversely affected by HTN. Among all the metabolic syndrome

TABLE III. Arterial Structure and Function by Blood Pressure Category

	NT (n=531)		Pre-HTN (n=65)		HTN (n=127)	
Variable	Mean	SD	Mean	SD	Mean	SD
Common cIMT, mm[a]	0.50	0.09	0.51	0.10	0.53	0.10
Bulb cIMT, mm[b]	0.49	0.10	0.50	0.13	0.54	0.10
Internal cIMT, mm[b]	0.40	0.09	0.44	0.10	0.44	0.10
Peterson, mm Hg[b]	184.4	55.3	202.3	57.8	221.8	81.5
YEM, mm Hg/mm[b]	268.5	128.2	304.9	115.5	308.5	132.7
AIx, %[c]	0.69	11.52	3.89	10.21	9.35	10.62
BrachD, mm Hg, % change[d]	6.16	1.31	5.75	1.21	5.32	1.11
PWVf, m/s[c]	5.75	0.92	6.38	1.06	7.12	1.25

Abbreviations: AIx, augmentation index; BrachD, brachial artery distensibility; cIMT, carotid intima-media thickness; HTN, hypertension; NT, normotension; PWVf, femoral pulse wave velocity; SD, standard deviation; YEM, Young's elastic modulus. $P<.05$ for [a]NT<HTN; [b]NT<pre-HTN and HTN; [c]NT<pre-HTN<HTN; [d]HTN<pre-HTN<NT.

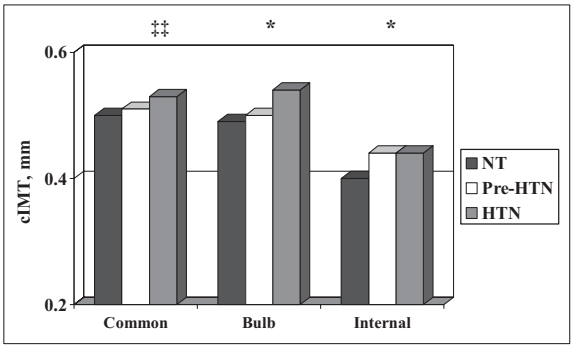

FIGURE 2. Carotid intima-media thickness (cIMT) by blood pressure group. $P<.05$ for ‡‡normotension (NT)<hypertension (HTN); *NT<pre-HTN and HTN.

components, HTN carried the greatest odds ratio (1.43; confidence interval, 1.27–1.60) for presence of carotid plaque, a risk factor for stroke, in a large study of Japanese patients aged 19 to 88 years.[54] However, HTN is also linked to early carotid changes. cIMT increased across BP categories in all race and sex groups in the Atherosclerosis Risk in Communities (ARIC) study,[55] a finding replicated in other large population-based studies.[56,57] Presence of HTN also predicts progression of cIMT,[58,59] so it is not surprising that greater carotid thickness can be found in adults with pre-HTN[35,60] and normal adults with multiple CV risk factors,[61] with a 0.058-mm increase in cIMT seen per 1-SD (21-mm Hg) increase in BP in a multi-ethnic study by Psaty and colleagues.[62]

The adverse changes in carotid structure seen in hypertensive adults are accompanied by parallel deterioration in carotid function. The ARIC study found that increased carotid stiffness predicted development of HTN[3] and that HTN was associated with increased carotid stiffness.[63] However, as in earlier studies,[64] the increase in stiffness was dependent on baseline distending pressure. In contrast, other investigators have found the hypertensive-related increase in carotid stiffness to be independent of baseline pressure but only in younger hypertensives.[65] HTN may have a stronger effect on arterial stiffness in younger individuals, while age and other CV risk factors may be more important at older ages. Data demonstrating that pre-hypertensive men, if young, have lower carotid distensibility than controls[66] support this hypothesis. It is possible that other age-related risk factors have a more powerful effect on carotid stiffness than BP at older ages.

Recent studies have demonstrated a relationship between BP and carotid structure and function in youth. Children referred to an HTN clinic were found to have thicker common carotid artery cIMT compared with controls. In two studies, the relationship was not independent of BMI.[67,68] However, other investigators have found the relationship between BP and cIMT to be significant even when adolescents are matched by BMI[69] or when statistical adjustment for adiposity is performed.[70] In a large recent study from our group, we found that the obesity-independent relationship between BP and cIMT also existed for the carotid bulb and internal carotid artery segments.[71] A few studies have related increased carotid stiffness to HTN in youth.[72] However, one investigator found the relationship only when lean controls, rather than obese controls, were compared with the hypertensive youth.[68] Two other studies found the relationship to be obesity-independent.[71,73] Our current paper extends these observations by providing data on all 3 carotid artery segments and examining the effect of both HTN and pre-HTN on carotid artery thickness and stiffness.

The majority of studies relating BP to arterial stiffness measure PWV. PWV is a robust measure that not only predicts CV events,[74,75] but also CV mortality.[76] Indeed, increased arterial stiffness, including faster PWV,[77] has been found with greater CV risk such as in HTN. There are also some limited data relating HTN in adults to higher AIx[78,79] and lower BrachD values.[80] Unfortunately, treatment of HTN in adulthood may not normalize PWV,[81] and annual rates of progression of PWV are higher in hypertensives compared with controls even if BP is well-controlled.[82] Underlying abnormalities in arterial stiffness may be contributing to development of HTN,[83] which then causes further deterioration in arterial elasticity. Higher PWV[84] and AIx[85] values have also been documented in pre-hypertensive adults. PWV gradually increased as a function of BP classification from normal HTN to pre-HTN to stage II HTN in one study.[86] Furthermore, studies of normotensive young adults with a positive family history of HTN have demonstrated lower BrachD[80] and higher PWV[87,88] and AIx[89] values, suggesting an underlying genetic

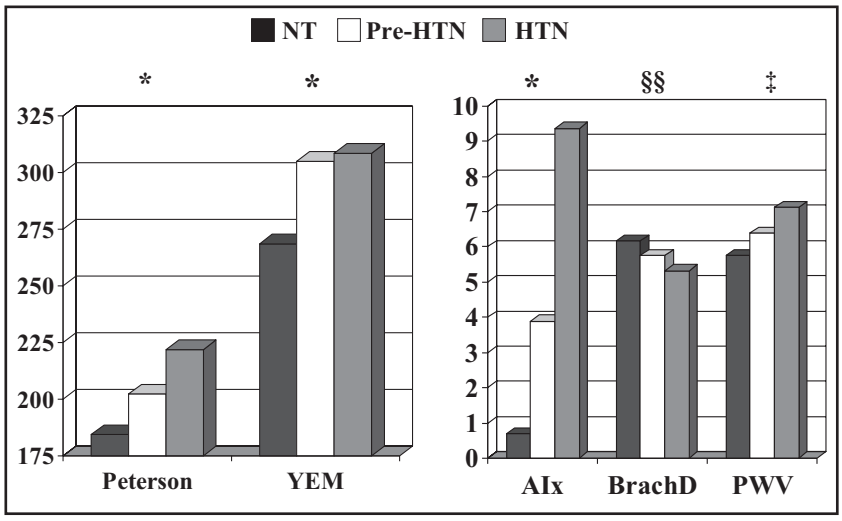

FIGURE 3. Arterial stiffness by blood pressure group. YEM indicates Young's elastic modulus; AIx, augmentation index; BrachD, brachial artery distensibility; PWV, pulse wave velocity. $P<.05$ for mean differences by analysis of variance. *Normotension (NT)<pre-hypertension (pre-HTN) and HTN; ‡NT<pre-HTN<HTN; §§HT<pre-HTN<HTN.

TABLE IV. Multivariable Models Indicating Independent Determinants of Cardiac Structure and Function

Variable	LVMI	RWT	E/A Ratio	E/Ea Lateral Ratio	E/Ea Septal Ratio	Ea/Aa Lateral Ratio	Ea/Aa Septal Ratio	Average Lateral and Septal Ea/Aa Ratios	E/Average Ea Lateral and Septal
Intercept	3.21	0.20	5.49	4.34	6.65	10.68	7.51	35.49	5.86
BP category									
NT	−0.06			−0.45				−0.46	
Pre-HTN	−0.063			−0.38				−0.29	
HTN[a]	0			0				0	
Age	0.0047					−0.026	−0.044		
Female	−0.1	−0.010							
Non-white race								−0.58	0.27
T2DM			−0.16	0.44	0.64			−0.68	0.52
BMI *z* score	0.075		0.13		0.50	−1.61	−0.11		0.37
Waist/height ratio	0.88	0.12	−1.08	2.95				−1.81	
MAP			−0.54			−1.25	−0.81	−4.27	
Heart rate	−0.0033		−0.010			−0.017	−0.011		
LDL-C								−0.008	
HDL-C								0.016	
TG		0.010							
Fasting glucose									
Fasting insulin							−0.108		
CRP						0.08			
R^2	0.52	0.1	0.12	0.16	0.17	0.19	0.3	0.2	0.21

Abbreviations: BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; LVMI, left ventricular mass index; MAP, mean arterial pressure; NT, normotension; RWT, relative wall thickness; T2DM, type 2 diabetes mellitus; TG, triglycerides. [a]0 indicates HTN group treated as reference group. All models have $P<.0001$ except Ea/Aa septal $P<.007$, and all parameter estimates listed have $P<.05$.

tendency for vascular dysfunction that may impact risk for developing HTN. Therefore, to prevent development of sustained HTN, it may be useful to assess arterial stiffness in high-risk individuals.

Arterial stiffness assessment is being performed in increasing numbers of pediatric studies. As in adults, most pediatric studies focus on PWV although normative data remain sparse. A recent study by Reusz and

TABLE V. Multivariable Models Indicating Independent Determinants of Arterial Structure and Function

						AIx	BrachD	PWV
Variable	Common	Bulb	Internal	PEM	YEM	(Higher=Stiffer)	(Lower=Stiffer)	(Higher=Stiffer)
Intercept	−0.84	−2.05	−1.39	4.83	4.60	−31.29	1.89	−0.77
BP category								
NT			−0.045	−0.086	−0.12	−3.61	0.29	−0.061
Pre-HTN			0.022	−0.046	−0.014	−3.76	−0.03	−0.036
HTN[a]			0	0	0	0	0	0
Age * BP category								
NT							−0.013	
Pre-HTN							0.003	
HTN[a]								
Age	0.011	0.0093	0.016	0.022			0.0064	0.014
Female	−0.097	−0.051	−0.12	−0.087			0.015	
Non-white race	0.059		0.052		−0.12			0.070
T2DM	0.066	0.055						
Height						−0.32		
BMI *z* score			0.020	0.036			−0.088	
Waist/height ratio					1.10			0.50
MAP		0.29			0.43	27.89	−0.0025	0.37
Heart rate		−0.0020						
LDL-C		0.00065	0.001					
TG						1.97		
Fasting glucose			0.055		−0.25			0.065
Fasting Insulin				0.051	−0.091		−0.0025	
Counts/non 0 min						−6.42		
R^2	0.16	0.11	0.20	0.16	0.17	0.25	0.43	0.60

Abbreviations: AIx, augmentation index; BMI, body mass index; BP, blood pressure; BrachD, brachial artery distensibility; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; NT, normotension; PEM, Peterson's elastic modulus; T2DM, type 2 diabetes mellitus; TG, triglycerides; YEM, Young's elastic modulus. [a]0 indicates HTN group treated as reference group. All Models have $P<.0001$.

colleagues provided PWV results on 1008 healthy patients (6–20 years) obtained with a similar method as employed in our study.[90] They found a strong correlation between BP and PWV, although no multivariable analyses correcting for other CV risk factors were performed.[90] Our previous data on 670 adolescents and young adults demonstrated that mean arterial pressure remained a predictor of PWV (and AIx and BrachD) even after correcting for adiposity, metabolic abnormalities (glucose, insulin, type 1[91] or type 2[26] diabetes), and inflammation. A few studies have specifically evaluated the relationship between BP classification and PWV including one that found higher PWV in pre-hypertensive adolescents compared with controls, but only in Caucasians.[92] Our data found higher PWV in pre-hypertensive non-Caucasians; however, we measured the standard carotid-femoral PWV. In the Zhu and colleagues paper,[92] carotid to dorsalis pedis was measured, and it is known that PWV is higher in smaller leg vessels compared with the central aorta.[26] A study examining younger children, mean age of 11.4 years, demonstrated higher PWV in patients with systolic BP $\geq$90th percentile, the cut-point for pre-HTN, compared with normotensives.[93] However, the investigators did not determine whether differences existed between pre-HTN and true HTN. Our findings confirm the graded increase in PWV from normo-HTN to pre-HTN to HTN in youth. We also provide BP level–stratified data for AIx and BrachD, techniques previously employed to investigate other CV risk factors in youth such as diabetes[94] and metabolic syndrome,[95] but not used for pediatric HTN research to date.

Limitations

Our finding of a graded increase in the prevalence of TOD across the BP strata, although cross-sectional, suggests that progression to higher levels of BP increases CV risk at a young age. However, our cross-sectional findings need to be confirmed in longitudinal studies. Furthermore, due to our study design, our population had a high prevalence of obesity and T2DM. However, BP classification remained an independent predictor of all the TOD measures even in multivariable models where BMI and presence of diabetes were entered as covariates. Furthermore, the prevalence of both obesity and T2DM are increasing around the globe. Therefore, our data point to the importance of modifying CV risk factors in high-risk youth even if only at borderline levels.

Some studies have suggested that the relationship between BP and arterial stiffness merely reflects the effect of increased distending pressure on the vessel.[63] Investigations of brachial arterial compliance under

isobaric conditions demonstrating impaired vascular function in hypertensives refute this assertion.[96,97] Furthermore, our model controlled for MAP and still found an effect of BP group on BrachD, suggesting that the effect was independent of baseline pressure.

There is much controversy on the appropriate method to index LVM to correct for differences in body size. Some studies have shown that fat-free body mass is more closely related to LVM than other anthropometric measures.[46,98,99] We chose to index LVM to height$^{2.7}$ because measurement of fat-free mass requires specialized equipment not readily available to many physicians and because the de Simone method of indexing LVM[20] has produced a sex-independent partition value of 51 g/m$^{2.7}$ that has proven better at predicting incident CV events[4,99] compared with other allometric adjustments, including indexing to height$^{1.7}$ suggested by[4,100] Chirinos and colleagues,[101] which was only superior in predicting all-cause mortality.

CONCLUSIONS

Our data provide additional support for the argument that BP has an important effect on the CV system in adolescents and young adults even with only modest elevation in BP (>90th percentile). This supports the concept that pediatricians should be prospectively identifying children and adolescents with BP >90th percentile and should begin lifestyle intervention earlier to prevent cardiac and vascular consequences. This also suggests that it may be necessary to consider implementation of pharmacologic intervention earlier and at a lower BP to prevent progression to sustained HTN as documented in the adult Trial of Preventing Hypertension (TROPHY) study.[102] This is especially important as these target organ changes may well be part of a vicious cycle that leads to further increases in BP and greater target organ disease. Longitudinal trials addressing the issue of earlier treatment based on intermediate noninvasive CV end points rather than using arbitrary cutpoints are needed.

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